OFFICE OF HUMAN RESEARCH ETHICS -- Institutional Review Board

INSTRUCTIONS FOR APPLICATION FOR IRB APPROVAL OF HUMAN SUBJECTS RESEARCH

Version June 25, 2009

What is the purpose of this form?

This application is to seek *initial* IRB approval for a research study.

What parts of this application should you submit?

Answer all questions, or mark "not applicable," when appropriate. Do not alter wording or delete questions from this form.

- For ***all studies***, submit Part A, which consists of these sections:
  - Part A.1. Contact Information, Agreements, and Signatures
  - Part A.2. Summary Checklist
  - Part A.3. Conflict of Interest Questions and Certification
  - Part A.4. Questions Common to All Studies
  - Part A.5. The Consent Process and Consent Documentation (including Waivers)

- For ***studies that involve direct interaction*** with human subjects (any contact with subjects including questionnaires, interviews, focus groups, observation, treatment interventions, etc), submit:
  - Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

- For ***studies*** that use existing data, records or human biological specimens, including for use in identifying potential subjects, submit:
  - Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

Note: You should submit Parts B or C only as applicable. If the study involves *both* direct interaction *and* use of existing materials, use both Parts B and C in addition to Part A.

Who can serve as principal investigator (PI)?

The PI is the person who will personally conduct or supervise this research study. Under most circumstances, this will be a faculty member. For IRB communication purposes, a trainee/student may be listed as PI. However, a faculty advisor must be identified, who holds ultimate responsibility for ensuring that this project complies with all University, regulatory, and fiscal requirements.

→ *See next page for additional instructions*

---- Instructions – Do not submit this page with your application ----

page 2 of instructions

Complete submission instructions can be found at http://ohre.unc.edu/submission_instructions.php. **All application and consent materials must be copied or printed on one side only**. See the checklist on page 1 of the application itself for items to include and number of copies.

Some applications require additional review prior to the IRB submission. Examples include the Clinical and Translational Research Center (formerly the GCRC and CCCT facilities) http://tracs.unc.edu/index.php?option=com_content&view=article&id=285&Itemid=312) or the Oncology Protocol Review Committee (PRC; http://cancer.med.unc.edu/research/prc/default.asp). See their web sites for details.

Many schools, departments, centers and institutes in Academic Affairs have local review committees that review before the IRB. See http://ohre.unc.edu/submission_instructions.php for a list of these units or consult your own unit for details.

Address for all Applications and Other Correspondence

IRB
CB# 7097, Medical Building 52
105 Mason Farm Road
Chapel Hill, NC 27599-7097

Types of Review

There are three levels of IRB Review (full board, expedited, and exempt), determined by the nature of the project, level of potential risk to human subjects, and the subject population. *The type of review applicable to a particular study is determined by the IRB.* Regardless of the kind of review, all applications use the same submission form.

Exempt and expedited review can be given to studies that constitute no more than minimal risk to the human subjects, i.e., the risk one experiences in daily living. These reviews are done in the IRB office on a continual basis.

Full board review is required for studies that involve greater than minimal risk or vulnerable populations that require special protection by the IRB. These require review by the convened IRB. See http://ohre.unc.edu/guide_to_irb.php for additional guidance.

---- Instructions – Do not submit this page with your application ----

OFFICE OF HUMAN RESEARCH ETHICS
Institutional Review Board

APPLICATION FOR IRB APPROVAL OF
HUMAN SUBJECTS RESEARCH
Version June 25, 2009

Part A.1. Contact Information, Agreements, and Signatures

Date: August 1, 2011

Title of Study: An Epidemiologic Health Study of Manganese Exposure in adult residents of East Liverpool, Ohio

Name and degrees of Principal Investigator: Danelle T. Lobdell, Ph.D.
Department: U.S. Environmental Protection Agency Mailing address/CB #: 7315
U.S. EPA Human Studies Facility 104 Mason Farm Rd
UNC-CH PID: Pager:
Phone #: 919-843-4434 Fax #: 919-966-7584 Email Address: Lobdell.danelle@epa.gov

For trainee-led projects: __ graduate __ postdoc __ resident __ other
Name of faculty advisor:
Department: Mailing address/CB #:
Phone #: Fax #: Email Address:

Center, institute, or department in which research is based if other than department(s) listed above:

Name of Project Manager or Study Coordinator (if any):

List **all other project personnel** including co-investigators, and anyone else who has contact with subjects or identifiable data from subjects. **Include name, location (UNC or specific outside location), role and email address for each person who should receive electronic copies of IRB correspondence to PI.**

Collaborators
Edward Hudgens – Project Officer on Contract
B. Michael Ray – QA officer (listed in UNC ethics training as "Billy Ray")

NOTE: This application is part of a study that U.S. EPA has funded through a contract to Rosemarie Bowler from San Francisco State University. This study has already been approved from SFSU IRB. Attached to this application is that package. SFSU will be the IRB of record for oversight. Dr. Lobdell is participating as the technical expert on the contract for EPA, thus is submitting to her IRB of record. Her role in the study is to provide the federal scientific oversight on the study. Because this is a contract, she has directed SFSU on the general exposure and outcomes the study will explore. SFSU has provided the detailed study protocol in which Dr. Lobdell has advised and approved. She will be at the study sight during data collection, but will not be engaged in any of the data collection procedures (e.g., consent, questionnaire, neurologic

testing, etc.). Her role is to provide federal oversight and to answer any questions that relate to the federal government. At the conclusion of the contract, Dr. Lobdell will receive the data collected from this study (ID only data, no names) at which time will explore secondary data analyses on other potential study questions. The main study questions will be analyzed and interpreted by Dr. Bowler's study team and Dr. Lobdell will be a co-author on those papers.

Name of funding source or sponsor (*please do not abbreviate*): United States Environmental Protection Agency
__ not funded X Federal __ State __ industry __ foundation __ UNC-CH
__ other (specify):

For external funding, RAMSeS proposal number (from Office of Sponsored Research): N/A

For industry sponsored research (if applicable):

Sponsor's master protocol version #: Version date:

Investigator Brochure version #: Version date:

Any other details you need documented on IRB approval:

Checklist of Items to Include with Your Submission

Include the following items with your submission, where applicable.

- Check the relevant items below and include one copy of all checked items 1-11 in the order listed.
- Also include two additional collated sets of copies (sorted in the order listed) for items 1-6.

Applications must "stand alone" and should provide all information requested, i.e., complete answers must be contained in the application. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

Applications will be returned if these instructions are not followed.

Check	Item	Total No. of Copies
□	1. This application. One copy must have original PI signatures.	3
□	2. Consent and assent forms (include DHHS-approved sample, when one exists), fact or information sheets, phone and verbal consent scripts.	3
□	3. HIPAA authorization addendum to consent form.	3
□	4. All recruitment materials including final copies of printed advertisements, audio/video taped advertisements, scripts, flyers, letters, and emails.	3
□	5. Questionnaires, focus group guides, scripts used to guide phone or in-person interviews, etc.	3
□	6. Documentation of reviews from any other committees (e.g., Clinical and Translational Research Center (CTRC), Oncology Protocol Review Committee, or local review committees in Academic Affairs).	3
□	7. Protocol, grant application or proposal supporting this submission, if any (e.g., extramural grant application to NIH or foundation, industry protocol, student proposal). If there is a cover sheet for the grant proposal it is to be included. These must be submitted if an external funding source or sponsor is checked on the previous page.	1
□	8. Addendum for Multi-Site Studies where UNC-CH is the Lead Coordinating Center.	1
□	9. Data use agreements (may be required for use of existing data from third parties).	1
□	10. Only for those study personnel *not* in the online UNC-CH human research ethics training database (http://cfx3.research.unc.edu/training_comp/): Documentation of required training in human research ethics.	1
□	11. For drug studies, Investigator Brochure if one exists. If none, include package insert for previously approved uses..	1

Principal Investigator: I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

Signature of Principal Investigator | Date

Note: The following signature is not required for applications with a student PI.

Department or Division Chair, Center Director (or counterpart) of PI: (or Vice-Chair or Chair's designee if Chair is investigator or otherwise unable to review): I certify that this research is appropriate for this Principal Investigator, that the investigators are qualified to conduct the research, and that there are adequate resources (including financial, support and facilities) available. If my unit has a local review committee for pre-IRB review, this requirement has been satisfied. I support this application, and hereby submit it for further review.

Signature of Department Chair or designee | Date

Print Name of Department Chair or designee | Department

Part A.2. Summary Checklist *Are the following involved?*	Yes	No
A.2.1. Existing data, research records, patient records, and/or human biological specimens?	x	__
A.2.2. Surveys, questionnaires, interviews, or focus groups with subjects?	x	__
A.2.3. Videotaping, audiotaping, filming of subjects, or analysis of existing tapes?	__	x
A.2.4. Do you have specific plans to enroll subjects from these vulnerable or select populations:		
a. UNC-CH students or UNC-CH employees?	__	x
b. Non-English-speaking?	__	x
c. Decisionally impaired?	__	x
d. Patients?	__	x
e. Prisoners, others involuntarily detained or incarcerated, or parolees?	__	x
f. Pregnant women?	__	x
g. Minors (less than 18 years)? ***If yes***, give age range: to years	__	x_
A.2.5. a. Are sites outside UNC-CH engaged in the research?	x	__
b. Is UNC-CH the sponsor or lead coordinating center for a multi-site study?	__	x
If yes, include the ***Addendum for Multi-site Studies***.		
If yes, will any of these sites be outside the United States?	__	__
If yes, is there a local ethics review committee agency with jurisdiction? (provide contact information)	__	__
A.2.6. Will this study use a data and safety monitoring board or committee?	__	x
If yes: UNC-CH NC TraCS DSMB? (must apply separately)	__	__
Lineberger Cancer Center DSMC?	__	__
Other? Specify:	__	__
A.2.7. a. Are you collecting sensitive information such as sexual behavior, HIV status, recreational drug use, illegal behaviors, child/physical abuse, immigration status, etc?	__	x
b. Do you plan to obtain a federal Certificate of Confidentiality for this study?	__	__
c. Is this research classified (e.g., requires security clearance)?	__	__
A.2.8. a. Investigational drugs? (provide **IND #**)	__	x
b. Approved drugs for "non-FDA-approved" conditions?	__	__
All studies testing substances in humans must provide a letter of acknowledgement from the UNC Health Care Investigational Drug Service (IDS).		
A.2.9. Placebo(s)?	__	x
A.2.10. Investigational devices, instruments, machines, software? (provide **IDE #**)	__	x
A.2.11. Fetal tissue?	__	x
A.2.12. Genetic studies on subjects' specimens?	__	x
A.2.13. Storage of subjects' specimens for future research? ***If yes***, *see instructions for* ***Consent for Stored Samples***.	x	__
A.2.14. Diagnostic or therapeutic ionizing radiation, or radioactive isotopes, which subjects would not receive otherwise? ***If yes***, *approval by the* ***UNC-CH Radiation Safety*** ***Committee*** *is required.*	__	x
A.2.15. Recombinant DNA or gene transfer to human subjects? ***If yes***, *approval by the* ***UNC-CH Institutional Biosafety*** ***Committee*** *is required.*	__	x
A.2.16. Does this study involve UNC-CH cancer patients? ***If yes***, *submit this application directly to the* ***Oncology Protocol Review Committee***.	__	x
A.2.17. Will subjects be studied in the Clinical and Translational Research Center (CTRC) or is the CTRC involved in any other way with this study? If yes, obtain the ***CTRC Addendum*** *and submit completed application (IRB application and Addendum) directly to the CTRC. The CTRC includes facilities located on the 3rd floor of the Main Hospital (formerly GCRC) and Ground floor Burnett-Womack (formerly CCCT).*	__	x
A.2.18. Will gadolinium be administered as a contrast agent?	..__	..x
A.2.19. Will subjects' Social Security Number (SSN) be collected for:		
a. processing payments greater than $200 per year, to support IRS reporting (see also B.6)?	__	x
b. processing payments of any amount through UNC-CH Accounts Payable?	__	x
c. use as a unique identifier for study tracking purposes for national registry or database?	__	x__

Part A.3. Conflict of Interest Questions and Certification

The following questions apply to **all investigators and study staff** engaged in the design, conduct, or reporting results of this project **and/or their immediate family members.** For these purposes, "family" includes the individual's spouse and dependent children. "Spouse" includes a person with whom one lives together in the same residence and with whom one shares responsibility for each other's welfare and shares financial obligations.

A.3.1. Currently or during the term of this research study, does any member of the research team or his/her family member have or expect to have:		
(a) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with the sponsor of this study?	__ yes	_X_ no
(b) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
(c) A personal financial interest in or personal financial relationship (including gifts of cash or in-kind) with an entity engaged in the performance of this project as a subcontractor, sub-recipient or vendor?	__ yes	_X_ no
(d) A board membership of any kind or an executive position (paid or unpaid) with the sponsor of this study or with an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no
A.3.2. Has the University or has a University-related foundation received a cash or in-kind gift from the sponsor of this study for the use or benefit of any member of the research team?	__ yes	_X_ no
A.3.3. Has the University or has a University-related foundation received a cash or in-kind gift for the use or benefit of any member of the research team from an entity that owns or has the right to commercialize a product, process or technology studied in this project?	__ yes	_X_ no

If the answer to ANY of the questions above is *yes*, the affected research team member(s) must complete and submit the form, which is accessible online at http://coi.unc.edu. List name(s) of all research team members for whom any answer to the questions above is *yes*:

_____

Certification by Principal Investigator: By submitting this IRB application, I (the PI) certify that the information provided above is true and accurate regarding my own circumstances, that I have inquired of every UNC-Chapel Hill employee or trainee who will be engaged in the design, conduct or reporting of results of this project as to the questions set out above, and that I have instructed any such person who has answered "yes" to any of these questions to complete and submit for approval a Conflict of Interest Evaluation Form. I understand that as Principal Investigator I am obligated to ensure that any potential conflicts of interest that exist in relation to my study are reported as required by University policy.

_____ _____

Signature of Principal Investigator Date

Part A.4. Questions Common to All Studies

For all questions, if the study involves only secondary data analysis, focus on your proposed design, methods and procedures, and not those of the original study that produced the data you plan to use.

Complete answers must be provided. While you may reference other documents with supporting information, do not respond solely by stating "see attached."

A.4.1. **Brief Summary**. Provide a *brief* non-technical description of the study, which will be used in IRB documentation as a description of the study. Typical summaries are 50-100 words. *Please reply to each item below, retaining the subheading labels already in place, so that reviewers can readily identify the content.*

Purpose: The purpose of this study is to assess if there are health effects associated with exposure to manganese (Mn) in air in adult residents of a Mn-exposed community.

Participants: 100 randomly selected long-term residents (≥10 years) of East Liverpool, Ohio between the ages of 30 to 75 years

Procedures (methods): Participants will be randomly selected within a 2.5-mile radius of the exposure source (a Mn warehousing and packaging facility) and appropriate exclusion criteria will be applied (see proposal). Following consent procedures, participants will be administered a battery of tests of cognitive function and motor efficiency. A brief neurological examination will be conducted using the Unified Parkinson's Disease Rating Scale (UPDRS). The Computerized Adaptive Testing System (CATSYS) will be used to assess postural sway and hand tremor. Whole blood will be analyzed for Mn, cadmium (Cd), mercury (Hg), and lead (Pb). Serum will be analyzed for ferritin and two liver enzymes. Hair samples and toenail clippings will be analyzed for Mn levels. Additionally, participants will be asked to complete questionnaires enquiring about their demographic information, mood, diet, occupational history, behavioral habits, and health history. Data collected from East Liverpool participants will be compared with previously collected data from the demographically similar, but less Mn-exposed town of Marietta, Ohio and the comparison town of Mount Vernon, Ohio where Mn exposure is not of concern.

The present study and its protocols have already been approved by SFSU Institutional Review Board (IRB) (see enclosed approval form). The study also has been described to all of the interested and collaborating stake holders (Ohio Department of Health, Ohio EPA, resident groups, health department officials, etc.) and the U.S.EPA and ATSDR.

A.4.2. **Purpose and Rationale**. Provide a summary of the background information, state the research question(s), and tell why the study is needed. If a complete rationale and literature review are in an accompanying grant application or other type of proposal, only provide a brief summary here. If there is no proposal, provide a more extensive rationale and literature review, including references.

For a more detailed description, please see the enclosed proposal.

Manganese is a naturally occurring essential element and low levels of Mn in water, food, and air are ubiquitous. In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners, steel and alloy smelters, chemical plant workers over-exposed to Mn, and iron/steel welders are known to be at risk for developing a pattern of signs and symptoms showing a decline in psychiatric health (i.e. mood disturbance), deterioration of cognitive ability (i.e. problems with attention, memory, and information processing), and a movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, dystonia, bradykinesia, and tremor) (Bowler et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. Although recent studies on children exposed to Mn- through drinking water show decrements in neuropsychological performance, none of the recent environmental studies on adults included comprehensive neuropsychological function testing in residents of living areas with air measurements, such as those detailed in the East Liverpool air reports. Only the earlier work by Mergler et al. (1999) related Mn in air to neuropsychological function. This present study seeks to fill that gap and will utilize past knowledge gained from these studies by using a more refined and recently updated neuropsychological test battery in addition to geo-coded data in relation to the Mn air results already performed by ATSDR and EPA in East Liverpool, Ohio.

The proposed study aims to answer the following questions:

- Is external Mn exposure (Mn-air) associated with biomarkers of internal Mn dose [Mn in blood (Mn-B), toenails (Mn-T), hair (Mn-H)] and neuropsychological and neurological function in adults?

- Does the neuropsychological function of a group of Mn-exposed adults differ significantly between groups with different levels of exposure to Mn-air?

This study will contribute to the knowledge of effects of environmental exposure at different levels to airborne Mn on neurological and neuropsychological functions of randomly selected adults.

A.4.3. **Subjects.** *You should describe the subject population even if your study does not involve direct interaction (e.g., existing records).* Specify number, gender, ethnicity, race, and age. Specify whether subjects are healthy volunteers or patients. If patients, specify any relevant disease or condition and indicate how potential subjects will be identified. Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., school principals, facility directors, hospital or healthcare system administrators).

The proposed health study will recruit 100 individuals residing within 2.5 miles of the Water Plant air monitor in East Liverpool, Ohio. Due to the similarities between East Liverpool and the two communities already studied (Marietta, Ohio and Mount Vernon, Ohio), the selected participants are expected to be similar on age, gender, ethnicity, and level of education (see Appendix C of the enclosed proposal).

A.4.4. **Inclusion/exclusion criteria.** List required characteristics of potential subjects, and those that preclude enrollment or involvement of subjects or their data. Justify exclusion of any group, especially by criteria based on gender, ethnicity, race, or age. If pregnant women are excluded, or if women who become pregnant are withdrawn, specific justification must be provided.

Inclusion criteria

To be included in the study, participants must be 30-75 years old and have 10 years or more of residency in East Liverpool. Participants must live in homes serviced by the municipal water supply and must reside within two miles of the Water Plant air monitor in East Liverpool, Ohio.

Exclusion criteria

1. Having had a major occupational exposure to pesticides, fungicides, or herbicides, carbon monoxide (CO), or other toxic metals requiring a medical visit;
2. A diagnosis of a psychiatric, neurological, or hepatic medical condition, including: stroke, electroconvulsive treatment, epilepsy, brain surgery, encephalitis, meningitis, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's dementia, schizophrenia, bipolar disorder;
3. Current treatment for alcohol or drug dependence;
4. Prior head injury or a stroke resulting in hospitalization for more than 1 day;
5. Having worked at S.H. Bell or Eramet Marietta Inc. at any time;
6. Women who are pregnant or nursing.

Pregnant and nursing women are excluded from the present study due to naturally occurring elevated levels of manganese in blood related to fetal development during pregnancy and the nutritional demands of breastfeeding. Mn biomarker results obtained from pregnant or nursing women would, therefore, not be representative of the community at large and would confound the interpretation of the data.

A.4.5. **Full description of the study design, methods and procedures.** Describe the research study. Discuss the study design; study procedures; sequential description of what subjects will be asked to do; assignment of subjects to various arms of the study if applicable; doses; frequency and route of administration of medication and other medical treatment if applicable; how data are to be collected (questionnaire, interview, focus group or specific procedure such as physical examination, venipuncture, etc.). Include information on who will collect data, who will conduct procedures or measurements. Indicate the number and duration of contacts with each subject; outcome measurements; and follow-up procedures. If the study involves medical treatment, distinguish standard care procedures from those that are research. If the study is a clinical trial involving patients as subjects and use of placebo control is involved, provide justification for the use of placebo controls.

Study Design: The proposed health study will utilize a cross-sectional design using a Mn-exposed group of 100 residents of East Liverpool drawn at random as an add-on to the 100 exposed residents from Marietta and 90 comparison residents from Mt. Vernon, who are part of a prior study currently being completed. As for the prior study, the same age group (30-75 years of age), and the same methods of selection/recruitment, inclusion and exclusion criteria, and neurological and neuropsychological test measures and procedures will be used in this current study of East Liverpool, Ohio.

RECRUITMENT

Participant recruitment will be preceded by public announcements of the study. The recruitment plan is outlined below.

a) Community Meetings and Health Study Announcements

1. Community meeting announcements will be made via radio, newspaper, and television.
2. The study P.I. and her assistant will travel to East Liverpool on September 14th, 2011 to meet with the Health Commissioner and her board, on September 15, 2011, presenting the study. The same evening, a meeting for the community will be held to describe the study as outlined below in # 3 open to the residents and other interested parties of East Liverpool.
3. The community meeting in East Liverpool will consist of a presentation of a brief slide show, previously presented at the Marietta, Ohio community meeting but revised for East

Liverpool. Around the time of the community meeting, invitation letters will be mailed to all the residents within a 1 mile radius from the Water Tower air monitor and to a random sample of approximately 1/3 of the residents in the 1-2.5 mile area, selected at random form a purchased list of postal addresses. The letter will describe the East Liverpool Community Health Study and its procedures. The letters will also contain a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview after the cards are received in the research office).

b) Recruitment Procedure:

1. The sample of households in the area of 2.5 miles surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from the 911 database, and a purchased list of all complete postal addresses.
2. Letters will be mailed to all residents within the 1 mile area from the Water Plant air monitor and a randomly selected group of addresses representing 1/3 of the database containing the postal addresses for the 1-2.5 mile area. The letters will contain a self-addressed, stamped card which could be used to indicate willingness to participate or denial to participate in the health study. If participants indicated interest, a brief questionnaire listing the exclusion factors will be administered during subsequent telephone calls to the participants. If the number of return cards received 2 weeks after the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book or the white pages. If the responses are insufficient in number, this process will be repeated until 110 adults are available to be tested or until the maximum number of phone calls has been reached for each potential participant (10 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).
3. Calls will be made until 110 individuals agree to participate.
4. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.
5. Two days prior to the appointment, telephone appointment reminder calls will be made.
6. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

Data collection methods: The same carefully controlled and standardized test administration instructions as those used in the Marietta/Mt Vernon study will be applied to the data collection procedures in East Liverpool. To the extent possible, the testers will be the same as in the prior study.

The data collected in this study will include the following:

1. Air exposure of Mn, already collected by the EPA/ATSDR for the period between 1999 and 2009 (9 years and 8 months).
2. Neuropsychological (including mood and motor efficiency) tests (see Appendix B of the enclosed proposal).

3. Neurological function will be assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) administered by the same trained physician (2 subscales: Activities of Daily Living and Motor Function)
4. The CATSYS (Danish Product Development) – consisting of 4 postural sway conditions and hand tremor.
5. A health questionnaire containing sections on residency, symptoms, medical history, medications, work history and behaviors, diet, and personal demographic information (enclosed).
6. The possibility of worry impacting symptom reporting in the East Liverpool group will be addressed in two ways: A) we will include an Environmental Worry Scale (EWS, enclosed), scores of which will be analyzed as a potential confounder and B) all examiners will be (most already are) trained in detecting symptom and cognitive impairment exaggeration. Additionally, a short test of effort (Rey-15) will be administered, which if failed, will result in the administration of a highly regarded test of symptom validity, the Victoria Symptom Validity Test (VSVT). This test is designed to provide evidence that can confirm or disconfirm the validity of an examinee's cognitive and symptom impairments. In the event that the examinee fails both the Rey 15 and the VSVT, that participant's test scores will be excluded from the group analysis.
7. Whole blood will be analyzed for levels of manganese (Mn), mercury (Hg), cadmium (Cd), and lead (Pb) and serum will be used to evaluate ferritin and the liver enzymes, alanine-aminotransferase (ALT) and gamma-glutamyltransaminase (GGT). Toenail and hair samples will be analyzed for levels of Mn. In total, 12 mL whole blood will be collected from each participant for analyses. Whole blood samples will be shipped on dry ice by Fed Ex immediately to the CDC and serum samples to the U.S. EPA NHEERL Core laboratories. The samples will be identified by each participant's ID number only and no names will be included
8.

STUDY PROCEDURES

1. The above recruitment methods will be followed.
2. Examiners will meet the day prior to testing and set up testing areas, review all test administrations and set up stations and offices where consent forms, interviews, and tests will be administered.
3. At the time the study will begin, scheduled study participants in groups (three groups per day) of 11 people (+ 1 extra person on one of the days) will be seated in a common area and greeted by the P.I. who will give a brief introduction about the study, the procedures, and the consent form.
4. Trained examiners will introduce themselves to participants and will explain the consent form in detail. Participants will be given time to ask questions. Then two copies of the informed consent will be signed; one for the participant and one for the researcher.
5. The P.I. will interview all of the participants with a brief, somewhat structured interview schedule, asking participants about special concerns, fears and observations related to their exposure. The check-out staff person will at this time collect and de-identify the participant's list of current medications, (copied each night at the conclusions of testing) which will be hand-carried in carry-on luggage by the P.I.
6. The participant will be invited to accompany one of the testers to a private room for testing. The neuropsychological testing will be conducted without any identifiers on the test protocols other than the respective I.D. number. Examiners will be two neuropsychologists and six graduate students in psychology, who will be trained by the

P.I. and senior staff (all have completed the course for the protection of human subjects – certificates enclosed).

7. After completion of the tests, the study staff will introduce participants to the certified phlebotomist, who will draw a total of 12 mL of venous blood from each participant for analysis. The Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory has agreed to perform the blood analyses of whole blood for Mn, Pb, Cd, and Hg levels. Ferritin levels, and ALT and GGT activities in serum will be determined by the U.S. EPA NHEERL Core laboratories. A total of 200 samples (two vials per participant, 6 mL each) of whole blood will be collected from study participants by the licensed and trained phlebotomist/medical technician. Presumably, one needle stick per participant (or as few as needed) will be used by the certified phlebotomist/medical technician. Four mL of whole blood will then be centrifuged at 800 x g for 10 min at room temperature to separate the serum. Whole blood will be kept at 4°C and serum samples will be immediately stored at -18°C until analysis and sent weekly by Express Mail to the laboratory. Half a milliliter of serum is needed for the analysis of ferritin concentrations by immunoturbidity using the Roche Tina-quant assay on the Hitachi 912 clinical analyzer. Also half a milliliter of serum is needed to analyse the activities of the liver enzymes ALT and GGT with a Beckman Synchron LX20 using an enzymic rate method. The usual QA/QC methods of the CDC Laboratory will be applied. Each analytic run is surrounded by at least two levels of bench quality control and one blind quality control sample is inserted with each run (40-60 samples). The methods are CLIA-certified and multiple PT are run, as available. The DLS QA/QC system (Caudill et al., 2008) is referred to as the Multi-Rule Quality Control System (MRQCS). The CDC rules are similar in nomenclature to Westgard's format, but the rules are not identical. Some of the additional features of MRQCS include the ability to distinguish between within-run and among-run precision, accommodating variable numbers of QC measurements per run and accommodating variable numbers of QC samples per pool. Quality control measures include analysis of initial calibration verification standard (National Institute of Standard and Technology standard reference material (NIST SRM) 1643e (trace elements in water, Gaithersburg, MD), a solution of NIST traceable 1 ng ml^{-1} manganese standard as the continuous calibration verification standard, procedural blank and Certified Reference material GBW 07601 (human hair) (Institute of Geophysical and Geochemical Exploration, Langfang, China) will be used as the quality control sample. Results will be given as the average of five replicate measurements of the instrument. Recovery of the analysis of QC standard by this procedure is 90% -110% and, precision is given as %RSD (SD*100/Mean) and for hair samples it varied from 1%-25%.
8. Hair samples will be collected using the following procedures: The collector will first evaluate the presence of sufficient hair on head for collection. Approx. 1-3 cm of hair should be available for collection. The scissors will be cleaned with an alcohol swab in front of the participant. Hair will be cut as close to the skull as possible from the base of the skull near the point halfway between the spine & ear (lower right or left quadrant). When enough mass is an issue, typically on men, smaller snips of hair will be taken in a random pattern. The side of hair sample that was close to the scalp will be marked by tying that end off with sewing thread and the collected hair will be placed into a small plastic bag with the participant's id clearly indicated on the bag. All small bags will be sealed and placed into a container and sent to the laboratory for analysis.
9. Toenail samples will be collected in the following manner: A pair of titanium dioxide nail clippers will be rubbed with alcohol swabs to be thoroughly cleaned between people.

Participants will be asked to clip their nails from all ten toes onto a clean paper (to make it easier to catch all the clippings) and place the collected nails in a small plastic bag labeled with their respective ID. All small bags will be placed into a container and send to the laboratory for analysis.

Whole sample (Hair/Toenails) will be pre-cleaned with 1% Triton X-100 solution prior to analysis to remove extraneous contaminants. Samples will be acid digested using ultra pure nitric acid at room temperature for 24 hours. Diluted samples will be analyzed for manganese using inductively coupled plasma mass spectrometry (ICP-MS, DRC-II, Perkin Elmer, Norwark, CT) using indium as the internal standard.

10. Two post-baccalaureate level students who were also part of the testing team in Marietta and Mt. Vernon, OH, will conduct check-in and check-out and review the questionnaires and individual participant folders to ascertain that all tests have been completed before the participant leaves. This protocol completeness review will be performed in order to detect unintentional omissions. Participants will at no time be pressured to answer any items they choose not to answer.
11. Upon completion of the study, a gift card for $50.00 for a local store will be presented to each participant as a token of appreciation for participation in the study.
12. Feedback of the group's results will be given to the community and all interested parties either in person or in written form during late summer of 2012. If additional funding becomes available, the P.I. will also present group results of the study in a community meeting in East Liverpool.
13. After the conclusion of the study, a brief feedback report will be prepared and mailed to each participant reporting the individual's test scores (by domain of function) and results of biomarker analyses. This report will also indicate whether the test results were:
    a) within the normal range
    b) of concern, needing a referral to the family physician for further assessment by specialists as indicated.
14. All relevant professional parties and city officials will be contacted and given feedback of the group's findings.
15. All inquiries by the media will be answered by the team of investigators including the P.I., Mr. Greg Stein from ODH and Dr. George Bollweg, representing the Regional U.S. EPA. Prior to any release of data, results and talking points will have been presented to the entire group of investigators, collaborators and advisory board for input and final wording.

A.4.6. **Benefits to subjects and/or society.** Describe any potential for direct benefit to individual subjects, as well as the benefit to society based on scientific knowledge to be gained; these should be clearly distinguished. Consider the nature, magnitude, and likelihood of any direct benefit to subjects. If there is no direct benefit to the individual subject, say so here and in the consent form (if there is a consent form). Do not list monetary payment or other compensation as a benefit.

Direct benefits to subjects

There are no direct benefits to participants.

Benefits to society

The study will address concerns about the potential health effects of Mn exposure by assessing the health status of a representative sample of East Liverpool residents. The study will provide important information about potential effects of gradients of exposure to Mn from industrial

sources in non-occupational environmental settings. Furthermore, the study will add to the limited literature on the relationship between various biomarkers of Mn (blood, toenails, hair).

A.4.7. **Full description of risks and measures to minimize risks.** Include risk of psychosocial harm (e.g., emotional distress, embarrassment, breach of confidentiality), economic harm (e.g., loss of employment or insurability, loss of professional standing or reputation, loss of standing within the community) and legal jeopardy (e.g., disclosure of illegal activity or negligence), as well as known side effects of study medication, if applicable, and risk of pain and physical injury. Describe what will be done to minimize these risks. Describe procedures for follow-up, when necessary, such as when subjects are found to be in need of medical or psychological referral. If there is no direct interaction with subjects, and risk is limited to breach of confidentiality (e.g., for existing data), state this.

- Drawing venous blood from the arm may cause minimal pain when the needle is inserted. There is also a slight risk of bruising and infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with these types of reactions. All possible accommodations will be made should this occur. Cutting a small amount of hair will be done with a blunted scissors which will prevent any accidental injuries. Blood samples will also be marked with an ID number only to ensure those analyzing the blood/serum are blinded to the identity of the participant. Arrangements will be made with a local physician on call, who will be recruited by a local colleague practicing in East Liverpool. The pager number and location of this local physician will be obtained so he/she may be contacted and available to address any medical emergency that may arise. Although such emergencies are highly unlikely, a participant, if necessary can be brought to the nearest Emergency Room at the local hospital.
- There is a risk of experiencing slight fatigue during testing. Testers are trained to look for signs of fatigue and a break will promptly be offered. The participants will also be informed that they can take a break or discontinue testing at any point.
- Participation may involve potential loss of privacy. To minimize this, results will be stored in a password-protected computer database with no identifying information attached. Hard copy files of all of the data will be kept by the P.I. in a locked file cabinet for 5 years with documents containing ID numbers only. Any documents or computer files linking ID numbers to names will be kept in a separate, locked file cabinet (or computer database) only accessible by the P.I. and will also be destroyed after 5 years.

A.4.8. **Data monitoring and analysis.** Tell how the qualitative and/or quantitative data will be analyzed. Explain how the sample size is sufficient to achieve the study aims. This might include a formal power calculation or explanation of why a small sample is sufficient (e.g., qualitative research, pilot studies). Describe the provisions for monitoring the data to ensure the safety of participants. These plans could range from the investigator monitoring subject data for any safety concerns to a sponsor-based DSMB, depending on the study.

In order to compare scores on neuropsychological, motor and mood tests, and the UPDRS between the three towns, the general linear model will be used. This will test for differences between participants in the three towns, including pairwise comparisons for differences in domains of neurological, neuropsychological, mood and motor functioning, with covariates included in the model as necessary. Logistic regressions will be used for dichotomous outcomes such as symptom and illness frequencies in each town, comparing the relative risk between the samples after controlling for the effects of covariates.

Multiple regression analyses will test for relationships between Mn levels in air, blood, hair, and toenails, and neuropsychological test scores in East Liverpool, and these relationships will be compared to the results recently obtained in Marietta. Logistic regressions will be used for categorical outcomes to examine the relationship between Mn levels in air and risk for particular illnesses or symptoms and mood.

Power analyses using G*Power statistical software indicated adequate statistical sensitivity with a sample size of 100. Setting power at 0.80 and alpha at 0.05, one-way between groups analyses of means would be powered to detect an effect size of f=.18 or greater. This is halfway between a small and medium effect size based on Cohen's (1988) guidelines, and should be sufficiently sensitive to detect the effects of manganese exposure in this sample, based on theory and previous research.

A.4.9. **Will you collect or receive any of the following identifiers?** Does not apply to consent forms.

__ No _**X**_ Yes *If yes, check all that apply*:

a. _**X**_ Names
b. _**X**_ Telephone numbers
c. _**X**_ Any elements of dates (other than year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death. For ages over 89: all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 and older
d. _**X**_ Any geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code
e. __ Fax numbers
f. _**X**_ Electronic mail addresses
g. __ Social security numbers
h. __ Medical record numbers
i. __ Health plan beneficiary numbers
j. __ Account numbers
k. __ Certificate/license numbers
l. __ Vehicle identifiers and serial numbers (VIN), including license plate numbers
m. __ Device identifiers and serial numbers (e.g., implanted medical device)
n. __ Web universal resource locators (URLs)
o. __ Internet protocol (IP) address numbers
p. __ Biometric identifiers, including finger and voice prints
q. __ Full face photographic images and any comparable images
r. __ Any other unique identifying number, code, or characteristic, other than dummy identifiers that are not derived from actual identifiers and for which the re-identification key is maintained by the health care provider and not disclosed to the researcher

A.4.10. **Identifiers in research data**. Are the identifiers in A.4.9 above linked or maintained with the research data?

__ yes _X_ no – only nonidentifiable ID numbers will be associated with the research data

A.4.11. **Confidentiality of the data**. Describe procedures for maintaining confidentiality of the data you will collect or will receive. Describe how you will protect the data from access by those not authorized. How will data be transmitted among research personnel? Where relevant, discuss the potential for deductive disclosure (i.e., directly identifying subjects from a combination of indirect IDs).

All test results will be linked to an ID number, with all personally identifying participant information removed. Results will be stored in an encrypted document on a password-protected computer and all paper materials will be stored in a locked file cabinet in the P.I.'s research office laboratory at 8371 Kent Drive, El Cerrito, CA 94530. Only Dr. Bowler will have access to information linking ID numbers and the identities of the participants. Each page in the participant's folder will be coded with an ID number only.

Security will be maintained by having an alarm system in the building and by having each staff member sign a special Data Contract to maintain confidentiality of the data, refraining from any public conversations about the participants. The data will not be released unless subpoenaed by a court of law. Anyone working on the data will also be required to sign this, guaranteeing confidentiality and guaranteeing that these data will not be used unless the P.I. is involved in order to guarantee privacy to the information given by the participant. All data will be maintained for approximately 5 years in hard copy, limiting access to only authorized individuals. The

electronic data will be securely stored indefinitely. Unauthorized access will be reported to the relevant parties (IRB, participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards, such as unique identification of authorized users, password protection, automated operating system patch (bug fix) management, anti-virus controls, firewall configuration, and scheduled and automatic backups to protect against data loss.

A.4.12. **Data sharing.** With whom will *identifiable* (contains any of the 18 identifiers listed in question A.4.9 above) data be shared outside the immediate research team? For each, explain confidentiality measures. Include data use agreements, if any.

_X_ No one
__ Coordinating Center**:**
__ Statisticians**:**
__ Consultants**:**
__ Other researchers**:**
__ Registries**:**
__ Sponsors:
__ External labs for additional testing:
__ Journals:
__ Publicly available dataset:
__ Other:

A.4.13. **Data security for storage and transmission**. Please check all that apply.

For electronic data stored on a desk top computer:
_X_ Secure network _X_ Password access __ Data encryption_X_ Password protected file(s)
__ Other comparable safeguard (describe):

For portable computing devices/external storage devices (e.g. laptop computer, PDA, CDs, memory sticks):
_X_ Power-on password __ Automatic log-off __ Data encryption _X_ Password protected file(s)
__ Other comparable safeguard (describe):

For hardcopy data (including human biological specimens, CDs, tapes, etc.):
_X_ Data de-identified by research team (stripped of the 18 identifiers listed in question A.4.9 above)
_X_ Locked suite or office _X_ Locked cabinet and Security Alarm in the Research Building
_X_ Data coded by research team with a master list secured and kept separately
__ Other (describe):

A.4.14. **Post-study disposition of identifiable data or human biological materials**. Describe your plans for disposition of data or human biological specimens that are identifiable in any way (directly or via indirect codes) once the study has ended. Describe your plan to destroy identifiers, if you will do so.

The CDC and US EPA laboratories are using the federally approved guidelines for maintenance and destructions of human biological specimens. All hard copies of data, including the list linking ID numbers with the names of participants, will be destroyed by shredding 5 years after the completion of the study.

Part A.5. The Consent Process and Consent Documentation (including Waivers)

The standard consent process is for all subjects to sign a document containing all the elements of informed consent, as specified in the federal regulations. Some or all of the elements of consent, including signatures, may be altered or waived under certain circumstances.

- If you will obtain consent in any manner, complete **section A.5.1**.
- If you are obtaining consent, but requesting a waiver of the requirement for a signed consent document, complete **section A.5.2**.
- If you are requesting a waiver of any or all of the elements of consent, complete **section A.5.3**.
- If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. This is addressed in section B.2.

You may need to complete more than one section. For example, if you are conducting a phone survey with verbal consent, complete sections A.5.1, A.5.2, and possibly A.5.3.

A.5.1. **Describe the process of obtaining informed consent from subjects**.
Describe who will be obtaining consent (or permission) and from whom. Include discussion, as relevant, any waiting period between the initial consent discussion and obtaining consent, and steps that will be taken to minimize coercion or undue influence. If children will be enrolled as subjects, describe the provisions for obtaining parental permission and assent of the child. If decisionally impaired adults are to be enrolled, describe the provision for obtaining surrogate consent from a legally authorized representative (LAR). If non-English speaking people will be enrolled, explain how consent in the native language will be obtained. Address both written translation of the consent and the availability of oral interpretation. It is expected that the information in the consent document(s) will be communicated to participants or their LAR. *After you have completed this part A.5.1, if you are not requesting a waiver of any type, you are done with Part A.5.; proceed to Part B.*

The study will first be introduced to East Liverpool residents at the community meeting that will take place in September 2011. A slide show detailing the study procedures for the community residents will be presented. Residents will be informed that they might receive a letter from the P.I. containing the study description. If selected, residents will be asked to complete and return a stamped, self-addressed card indicating willingness or non-willingness to participate to the P.I. Participants will be able to have their questions answered during the recruitment and screening calls, as well as later, at the time of the appointment. They will be able to ask the P.I. any additional questions that may arise either on site after the meeting or over the telephone when they are administered the inclusion/exclusion questionnaire. They also will be provided additional time to ask questions when the IRB approved consent forms are explained and reviewed by the examiners with each participant at the time of testing. The consent forms will be kept in each participant's testing protocol folder for the duration of the study procedure. Upon arrival at the P.I.'s office, the consent forms will be removed from the folders containing the

participants' test protocols and will be in possession of the P.I. , along with the list connecting IDs and names. These forms will be kept in a locked file cabinet in the P.I.'s office.

A.5.2. **Justification for a waiver of *written* (i.e., signed) consent**. *The default is for subjects to sign a written document that contains all the elements of informed consent.* Under limited circumstances, the requirement for a signed consent form may be waived by the IRB if either of the following is true. *Choose only one:*

a. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). *Participants should be asked whether they want documentation linking them with the research and the participants' wishes will govern whether they sign the form.* Note: This justification cannot be used in FDA-regulated research. __ yes __ no __ yes __ no

Explain.

b. The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., phone survey).

Explain.

If you checked "yes" to either (and you are not requesting a waiver in section A.5.3) consent must be obtained orally, by delivering a fact sheet, through an online consent form, or be incorporated into the survey itself. Include a copy of the consent script, fact sheet, online consent form, or incorporated document.

→ If you have justified a waiver of written (signed) consent (A.5.2), you should complete A.5.3 *only* if your consent process will not include all the other elements of consent.

A.5.3. **Justification for a full or partial waiver of consent.** *The default is for subjects to give informed consent.* A waiver might be requested for research involving only existing data or human biological specimens (see also Part C). More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavioral research involving deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA authorization if research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

__ Requesting **waiver of some elements** (specify; see SOP 28 on the IRB web site):
__ Requesting **waiver of consent entirely**

If you check either of the boxes above, answer items a-f.. To justify a full waiver of the requirement for informed consent, you must be able to answer "yes" (or "not applicable" for question c) to items a-f. **Insert brief explanations that support your answers.**

a. Will the research involve no greater than minimal risk to subjects or to their privacy? __ yes __ no

Explain.

b. Is it true that the waiver will *not* adversely affect the rights and welfare of subjects? *(Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)* __ yes __ no

Explain.

c. When applicable to your study, do you have plans to provide subjects with pertinent information after their participation is over? *(e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)* __ yes __ not applicable

Explain.

d. Would the research be impracticable without the waiver? *(If you checked "yes," explain how the requirement to obtain consent would make the research impracticable, e.g., are most of the subjects lost to follow-up or deceased?).* __ yes __ no

Explain.

e. Is the risk to privacy reasonable in relation to benefits to be gained or the importance of the knowledge to be gained? __ yes __ no

Explain.

If you are accessing patient records for this research, you must also be able to answer "yes" to item f to justify a waiver of HIPAA authorization from the subjects.

f. Would the research be impracticable if you could not record (or use) Protected Health Information (PHI)? *(If you checked "yes," explain how* not *recording or using PHI would make the research impracticable).* __ yes __ no

Explain.

Part B. Questions for Studies that Involve Direct Interaction with Human Subjects

→ ***If this does not apply to your study, do not submit this section.***

B.1. **Methods of recruiting.** Describe how and where subjects will be identified and recruited. Indicate who will do the recruiting, and tell how subjects will be contacted. Describe efforts to ensure equal access to participation among women and minorities. Describe how you will protect the privacy of potential subjects during recruitment. *For prospective subjects whose status (e.g., as patient or client), condition, or contact information is not publicly available (e.g., from a phone book or public web site), the initial contact should be made with legitimate knowledge of the subjects' circumstances. Ideally, the individual with such knowledge should seek prospective subjects' permission to release names to the PI for recruitment. Alternatively, the knowledgeable individual could provide information about the study, including contact information for the investigator, so that interested prospective subjects can contact the investigator*. Provide the IRB with a copy of any document or script that will be used to obtain the patients' permission for release of names or to introduce the study. Check with the IRB for further guidance.

Full descriptions of the study design, methods and procedures are included in the enclosed proposal. Participant recruitment will be preceded by public announcements of the study. The recruitment plan is outlined below.

a) Community Meetings and Health Study Announcements

4. Community meeting announcements will be made via radio, newspaper, and television.
5. The study P.I. and her assistant will travel to East Liverpool on September 14th, 2011 to meet with the Health Commissioner and her board, on September 15, 2011, presenting the study. The same evening, a meeting for the community will be held to describe the study as outlined below in # 3 open to the residents and other interested parties of East Liverpool.
6. The community meeting in East Liverpool will consist of a presentation of a brief slide show, previously presented at the Marietta, Ohio community meeting but revised for East Liverpool. Around the time of the community meeting, invitation letters to a large random sample of approximately 1/3 East Liverpool households, selected at random form a purchased list of postal addresses within two miles of the Water Plant air monitor will be mailed. The letter will describe the East Liverpool Community Health Study and its procedures. The letters will also contain a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview after the cards are received in the research office).

b) Recruitment Procedure:

7. The sample of households in the area of two miles surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from the 911 database, and a purchased list of all complete postal addresses for the 2 mile area west of the Water Tower Monitor and the S.H. Bell facility.
8. Letters will be mailed to a randomly selected group of addresses representing 1/3 of the database containing the postal addresses. The letters will contain a self-addressed, stamped card which could be used to indicate willingness to participate or denial to

participate in the health study. If participants indicated interest, a brief questionnaire listing the exclusion factors will be administered during subsequent telephone calls to the participants. If the number of return cards received 2 weeks after the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book or the white pages. If the responses are insufficient in number, this process will be repeated until 110 adults are available to be tested or until the maximum number of phone calls has been reached for each potential participant (10 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).

9. Calls will be made until 110 individuals agree to participate.
10. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.
11. Two days prior to the appointment, telephone appointment reminder calls will be made.
12. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

B.2. **Protected Health Information (PHI).** If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a *limited waiver of HIPAA authorization*. If this applies to your study, please provide the following information and complete Section C.

This study does not require a HIPPA consent form. We are not obtaining medical records, nor using medical data from those records.

a. Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. What information are you planning to collect for this purpose?

b. How will confidentiality/privacy be protected prior to ascertaining desire to participate?

c. When and how will you destroy the contact information if an individual declines participation?

B.3. **Duration of entire study and duration of an individual subject's participation, including follow-up evaluation if applicable.** Include the number of required contacts and approximate duration of each contact.

The study will take place over the course of 12 months and will include preparation, testing (data collection), data entry, data cleaning and analyses, and participant feedback and final reports. Participants might be directly involved in the study on the following occasions:

1. Receipt of a recruitment letter
2. Mailing of a stamped, pre-addressed postcard to indicate interest in participating
3. Screening telephone call – 10 min

4. Appointment scheduling telephone call – 5 min
5. Appointment reminder call – 3 min
6. Testing – 2.5- 4 hours
7. Receipt of feedback letter

B.4. **Where will the subjects be studied?** Describe locations where subjects will be studied, both on and off the UNC-CH campus.

The data collection part of the study (i.e. testing) will take place in a central location in East Liverpool, Ohio (the Motor Lodge Motel).

B.5. **Privacy.** Describe procedures that will ensure privacy of the subjects in this study. Examples include the setting for interviews, phone conversations, or physical examinations; communication methods or mailed materials (e.g., mailings should not indicate disease status or focus of study on the envelope).

To ensure privacy, all neuropsychological testing will be conducted in a private room with only the participant and examiner present. Collection of blood, toenail, and hair samples will also take place in a separate, private room, as will the CATSYS and UPDRS examinations. The P.I. will conduct a brief interview with each participant in a secluded area. No phone conversations with participants will be conducted in public – all phone conversations will take place in private office settings.

B.6. **Inducements for participation.** Describe all inducements to participate, monetary or non-monetary. If monetary, specify the amount and schedule for payments and if/how this will be prorated if the subject withdraws (or is withdrawn) from the study prior to completing it. For compensation in foreign currency, provide a US$ equivalent. Provide evidence that the amount is not coercive (e.g., describe purchasing power for foreign countries). Be aware that payment over a certain amount may require the collection of the subjects' Social Security Numbers. If a subject is paid more than $200.00 per year, collection of subjects' Social Security Number is required (University policy—see SSN Guidance) using the Social Security Number collection consent addendum found under forms on the IRB website (look for Study Subject Reimbursement Form).

Upon completion of the study, a gift card for $50.00 from a local store will be presented to each participant as a token of appreciation for participation in the study. This amount is not considered coercive. Due to limited funding, early withdrawal from the study or incompletion of major parts of the study will not be compensated monetarily.

B.7. **Costs to be borne by subjects.** Include child care, travel, parking, clinic fees, diagnostic and laboratory studies, drugs, devices, all professional fees, etc. If there are no costs to subjects other than their time to participate, indicate this.

There is no cost for taking part in the study, aside from the transportation costs of coming to the appointment. Transportation costs involved in coming to the facility, which will be selected to be convenient for participants, will not be reimbursed. The researchers, research team and sponsors of this project will not provide medical care nor cover the cost of medical care for participants.

Part C. Questions for Studies using Existing Data, Records or Human Biological Specimens

→ ***This section applies even if records are only used to identify potential subjects.***

→ ***If your study does not use existing data, records or specimens for any purpose, do not submit this section.***

C.1. What records, data or human biological specimens will you be using? *(check all that apply)*:

_X_ Data already collected for another research study
If applicant was involved in the original collection, please explain role:

The P.I. of the present study was also the principal investigator of the Marietta/Mount Vernon Health study, data from which will be used in the data analyses phase of the present study.

__ Data already collected for administrative purposes (e.g., Medicare data, hospital discharge data)
__ Medical records (custodian may also require form, e.g., HD-974 if UNC-Health Care System)
__ Electronic information from clinical database (custodian may also require form)
__ Patient specimens (tissues, blood, serum, surgical discards, etc.)
_X_ Other (specify):
Completely de-identified research data from the prior Marietta/Mount Vernon health study will be used.

C.2. For each of the boxes checked in 1, how were the original data, records, or human biological specimens collected? Describe the process of data collection including consent, if applicable.

The data collection process for the Marietta/Mount Vernon Health study was identical to the one outlined in the present study, with the exception of not including toenail and hair sample collected. The protocol, consent forms and scripts were reviewed and approved by the San Francisco State University IRB, 2 external reviewers on behalf of the U.S. EPA, and the Ohio Department of Health.

C.3. For each of the boxes checked in 1, where do these data, records or human biological specimens currently reside?

The non-identifiable data is currently in possession of the P.I.

C.4. For each of the boxes checked in 1, do you have permission from the custodians of the data, records or human biological specimens (e.g., pathology dept, tissue bank, original researcher)? Include data use agreements, if required by the custodian of data that are not publicly available.

N/A

C.5. If the research involves human biological specimens, has the purpose for which they were collected been met before removal of any excess? For example, has the pathologist in charge or the clinical laboratory director certified that the original clinical purpose has been satisfied? Explain if necessary.

__ yes __ no _X_ not applicable (explain)
The specimens collected previously were part of an epidemiologic examination, NOT from patient specimen excess. All the specimens have been tested and only the results of the already tested specimens will be used in this study.

C.6. Do *all* of these data, records or specimens exist at the time of this application? If not, explain how prospective data collection will occur.

_X_ no If no, explain